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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,350	07/11/2003	John K. Cini	MXI-285	6687

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,350	CINI ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-33,35-39,41 and 42* is/are pending in the application.

4a) Of the above claim(s) *2,5,7,8,22,24,27,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6, 9-15, 17-21, 23, 25, 26, 28-33, 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed on 07/28/2006 has been entered in full. Claims 1, 14-15, 17-20, 22-23, 32-33, 35-38, and 41-42 have been amended and claims 16,34, and 40 have been canceled. Claims 1-15, 17-33, 35-39, and 41-42 are pending. Claims 1, 3, 4, 6, 9-15, 17-21, 23, 25, 26, 28-33, 35-39 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 1, 4, 9, 10, 12, 13, 15, 20, 21, 23, 26, 29-31, 33, and 38-40 under 35 U.S.C. 102(b) as being anticipated by Foster et al. (US 5,217,954 A, 8 June 1993) has been withdrawn in view of amended claims.

Claims 1, 3, 4, 6, 9-13, 15, 21, 23, 25, 26, 28-31, 33, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Kerwin et al. (US Patent No. 5,929,031, 27 July 1999).

In view of amended claims, the rejection of claims 16-19 and 34-37 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 5,217,954 A, 8 June 1993),

and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000) has been replaced by a new 103 (a) rejection for clarity of the record.

In view of amended claims, the rejection of claims 14 and 32 under 35 U.S.C. 103(a) as being unpatentable over Kerwin et al. (US Patent No. 5,929,031, 27 July 1999), and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000) has been replaced by a new 103 (a) rejection for clarity of the record.

Information Disclosure Statement

The Information Disclosure Statement submitted on 07/28/2006 has been received by the Office and the listed references have been considered by the Examiner.

Claim Rejections under 35 USC §103 (a)

(i). Claims 1, 4, 9, 10, 12, 13, 15, 17-21, 23, 26, 29-31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 5,217,954 A, 8 June 1993), and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000).

Foster et al. teach protection of bFGF from oxidation during storage and clinical use. Foster et al. teach the presence of certain chelating agents effectively stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation (bottom of column 1). Specifically, Foster et al. teach preparation of a pharmaceutical

formulation comprising a protein, bFGF, a stabilizing chelator, such as DTPA or EGTA. The formulation comprises optionally an agent for tonicity, a preservative or other auxiliaries, such as mannitol, glycerol, sodium chloride (see, e.g., columns 3-6) or Tris (Example 1). The concentration of chelating agent is present in amounts of from about 0.001% to about 2.0% percent (weight/weight) of the overall formulation (the 4th paragraph of column 4), which is within the recited concentration of DTPA, about 1 μM to about 10 mM in claim 4. Foster et al. teach that the stabilizer can be used in combination with other stabilizers, such as citrate (the 2nd paragraph of column 5) and that the formulation can be prepared in a buffer system, such as sodium citrate (the 4th paragraph of column 5), with the pH of the formulation being from about 2 to about 8 (the 6th paragraph of column 5). Foster et al. teach continuous release formulations, including microcapsules that are essentially small particles of active compounds embedded in a suitable polymer (the 4th paragraph of column 5). Foster et al. further teach that the formulation comprises 0.01%-10% FGF in solution (lines 48-49 of column 6, and in Example 4, the concentration of FGF is 100 ug/ml).

Foster et al. do not teach preparing a formulation comprising an antibody, a monoclonal antibody or a human antibody.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a solution state (the

4th paragraph of column 1).

Therefore, it would have been obvious to one of skilled in the art to prepare a pharmaceutical composition comprising a human monoclonal antibody instead of FGF according to the methods taught by Foster et al. with a reasonable expectation of success. One would have been motivated to do so because a human monoclonal antibody is, in essence, a protein and both of them share the basic components—amino acids including cysteine residues, which are susceptible to oxidation. Moreover, a human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). Thus, the formulation taught by Foster et al. would stabilize a human monoclonal antibody.

Response to Applicants' Argument

Applicants review the legal standard for a prima facie case of obviousness and argue that Foster et al. teach the use of mannitol as a bulking agent in order to formulate FGF as a topical vehicle formulation. Applicants submit that Foster et al. fail to teach or suggest that mannitol may be used to prevent oxidation of proteins, e.g., antibodies.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the anti-oxidation property of mannitol is inherent to its structure and whether Foster et al. teach the antioxidation property of mannitol in the formulation is irrelevant to the issue here. The teachings of Foster et al. in combination with the teaching of

Hagiwara et al. would have motivated one of skilled in the art to prepare a pharmaceutical composition comprising a human monoclonal antibody instead of FGF according to the methods taught by Foster et al. In other words, the combined teachings of Foster et al. and Hagiwara et al. teach the same invention as that claimed by Applicants.

Applicants argue that Hagiwara et al. do not make up for aforementioned deficiencies in the primary reference of Foster et al. Applicants argue that Hagiwara et al. teach a stabilized human monoclonal antibody preparation containing mannitol. However, the mannitol taught by Hagiwara et al. is used as a bulking agent in order to permit lyophilization. Applicants submit that there is no teaching or suggestion in Hagiwara et al. with respect to the use of mannitol in preventing oxidation of antibodies.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the reference of Hagiwara et al. is cited here to provide teaching on an antibody. Thus, Applicants' argument is misplaced. It is noted that Applicants' argument that the mannitol taught by Hagiwara et al. is used as a bulking agent is inaccurate because Hagiwara et al. clearly teach the use of mannitol as a stabilizer (see, e.g., Table 1).

(ii). Claims 1, 3, 4, 6, 9-15, 21, 23, 25, 26, 28-33, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerwin et al. (US Patent No. 5,929,031, 27

July 1999), and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000).

Kerwin et al. teach preparation of a pharmaceutical composition (column 8), which comprises a protein, hemoglobin at a concentration of 0.001% to 90% (w/v) (4 mg/ml and 100 mg/ml were used in Example 1 and 2), a reducing agent, such as sodium ascorbate or 0.03% (w/v) polysorbate 80 (lines 24-25 of column 13), chelators, such as 0-200 μM of DTPA and/ or EGTA (lines 45-51 of column 8), 0-2 M of mannitol (lines 39-42 of column 8), which is within the range recited in claim 6. The formulation may also comprise one or more buffers, such as citrate or Tris (line 65 of column 12), and salts, such as sodium chloride (lines 32-35). The pH of the composition can be at about 6.5-9.5 (line 52 of column 8).

Kerwin et al. do not teach preparing a formulation comprising an antibody, a monoclonal antibody or a human antibody.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a solution state (the 4th paragraph of column 1).

Therefore, it would have been obvious to one of skilled in the art to prepare a

pharmaceutical composition comprising a human monoclonal antibody instead of hemoglobin according to the methods taught by Kerwin et al. with a reasonable expectation of success. One would have been motivated to do so because a human monoclonal antibody is, in essence, a protein and both of them share the basic components—amino acids, which are susceptible to oxidation. Moreover, a human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). Thus, the formulation taught by Kerwin et al. would stabilize a human monoclonal antibody.

Response to Applicants' Argument

Applicants review the legal standard for a prima facie case of obviousness and argue that Kerwin et al. fail to teach or suggest that mannitol may be used to prevent oxidation of proteins, e.g., antibodies.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the anti-oxidation property of mannitol is inherent to its structure and whether Kerwin et al. teach the antioxidation property of mannitol in the formulation is irrelevant to the issue here. The teachings of Kerwin et al. in combination with the teaching of Hagiwara et al. would have motivated one of skilled in the art to prepare a pharmaceutical composition comprising a human monoclonal antibody instead of hemoglobin according to the methods taught by Kerwin et al. In other words, the

combined teachings of Kerwin et al. and Hagiwara et al. teach the same product as that claimed by Applicants.

Applicants argue that Hagiwara et al. do not make up for aforementioned deficiencies in the primary reference of Kerwin et al. Applicants argue that Hagiwara et al. teach a stabilized human monoclonal antibody preparation containing mannitol. However, the mannitol taught by Hagiwara et al. is used as a bulking agent in order to permit lyophilization. Applicants submit that there is no teaching or suggestion in Hagiwara et al. with respect to the use of mannitol in preventing oxidation of antibodies.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the reference of Hagiwara et al. is cited here to provide teaching on an antibody. Thus, Applicants' argument is misplaced. It is noted that Applicants' argument that the mannitol taught by Hagiwara et al. is used as a bulking agent is inaccurate because Hagiwara et al. clearly teach the use of mannitol as a stabilizer (see, e.g., Table 1).

Claim Objections for Minor Informalities

The objection to claims 1, 3, 4, 9-13, 15, 17-21, 23, 28 for reciting non-elected species is maintained because the claims have not been amended to remove the non-elected species. Appropriate correction is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
October 14, 2006

RUIXIANG LI, PH.D.
PRIMARY EXAMINER